Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1644PNH

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Jan 25	BLAST(R) searching in REGISTRY available in STN on the Web
NEWS 3	Jan 29	FSTA has been reloaded and moves to weekly updates
NEWS 4	Feb 01	DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 5	Feb 19	Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS 6	Mar 08	Gene Names now available in BIOSIS
NEWS 7	Mar 22	TOXLIT no longer available
NEWS 8	Mar 22	TRCTHERMO no longer available
NEWS 9	Mar 28	US Provisional Priorities searched with P in CA/CAplus and USPATFULL
NEWS 10	Mar 28	LIPINSKI/CALC added for property searching in REGISTRY
NEWS 11	Apr 02	PAPERCHEM no longer available on STN. Use PAPERCHEM2 instead.
NEWS 12	Apr 08	"Ask CAS" for self-help around the clock
NEWS 13	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 14	Apr 09	ZDB will be removed from STN
NEWS 15	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 16	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 17	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 18	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 19	Jun 03	New e-mail delivery for search results now available
NEWS 20	Jun 10	MEDLINE Reload
NEWS 21	Jun 10	PCTFULL has been reloaded

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 08:27:25 ON 18 JUN 2002

```
=> file medline embase biosis scisearch caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                      0.21       0.21

FILE 'MEDLINE' ENTERED AT 08:27:43 ON 18 JUN 2002

FILE 'EMBASE' ENTERED AT 08:27:43 ON 18 JUN 2002
COPYRIGHT (C) 2002 Elsevier Science B.V.  All rights reserved.

FILE 'BIOSIS' ENTERED AT 08:27:43 ON 18 JUN 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'SCISEARCH' ENTERED AT 08:27:43 ON 18 JUN 2002
COPYRIGHT (C) 2002 Institute for Scientific Information (ISI) (R)

FILE 'CAPLUS' ENTERED AT 08:27:43 ON 18 JUN 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

=> s cyclic peptide
L1       10108 CYCLIC PEPTIDE

=> s l1 and monomeric
L2          66 L1 AND MONOMERIC

=> s l2 and monocyclic
L3           1 L2 AND MONOCYCLIC

=> d l3 cbib abs

L3   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
2001:545508   Document No. 135:132464  Cyclic peptide
     inhibitors of VEGF, VEGF-C, and VEGF-D, preparation methods,
     pharmaceutical compositions, and therapeutic use.  Achen, Marc G.; Hughes,
     Richard A.; Stacker, Steven; Cendron, Angela (Ludwig Institute for Cancer
     Research, USA).  PCT Int. Appl. WO 2001052875 A1 20010726, 102 pp.
     DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ,
     CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
     HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
     LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG,
     SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY,
     KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE,
     DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN,
     TD, TG, TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO 2001-US1533
     20010118.  PRIORITY: US 2000-PV176293 20000118; US 2000-PV204590 20000516.
AB   The invention provides monomeric monocyclic peptide
     inhibitors and dimeric bicyclic peptide inhibitors based on exposed loop
     fragments of a growth factor protein, e.g. loop 1, loop 2 or loop 3 of
     VEGF-D, as well as methods of making them, pharmaceutical compns. contg.
     them, and therapeutic methods of use.


=> s l2 and VEGF
L4           1 L2 AND VEGF

=> d l4 cbib abs

L4   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
2001:545508   Document No. 135:132464  Cyclic peptide
     inhibitors of VEGF, VEGF-C, and VEGF-D,
```

preparation methods, pharmaceutical compositions, and therapeutic use. Achen, Marc G.; Hughes, Richard A.; Stacker, Steven; Cendron, Angela (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001052875 A1 20010726, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1533 20010118. PRIORITY: US 2000-PV176293 20000118; US 2000-PV204590 20000516.

AB The invention provides **monomeric** monocyclic peptide inhibitors and dimeric bicyclic peptide inhibitors based on exposed loop fragments of a growth factor protein, e.g. loop 1, loop 2 or loop 3 of **VEGF** -D, as well as methods of making them, pharmaceutical compns. contg. them, and therapeutic methods of use.

=> s l2 and VEGF-C
L5 1 L2 AND VEGF-C

=> d l5 cbib abs

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:545508 Document No. 135:132464 **Cyclic peptide** inhibitors of VEGF, **VEGF-C**, and VEGF-D, preparation methods, pharmaceutical compositions, and therapeutic use. Achen, Marc G.; Hughes, Richard A.; Stacker, Steven; Cendron, Angela (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001052875 A1 20010726, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1533 20010118. PRIORITY: US 2000-PV176293 20000118; US 2000-PV204590 20000516.

AB The invention provides **monomeric** monocyclic peptide inhibitors and dimeric bicyclic peptide inhibitors based on exposed loop fragments of a growth factor protein, e.g. loop 1, loop 2 or loop 3 of VEGF-D, as well as methods of making them, pharmaceutical compns. contg. them, and therapeutic methods of use.

=> s VEGF-D
L6 288 VEGF-D

=> s l6 and cyclic peptide
L7 1 L6 AND CYCLIC PEPTIDE

=> d l7 cbib abs

L7 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:545508 Document No. 135:132464 **Cyclic peptide** inhibitors of VEGF, VEGF-C, and **VEGF-D**, preparation methods, pharmaceutical compositions, and therapeutic use. Achen, Marc G.; Hughes, Richard A.; Stacker, Steven; Cendron, Angela (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001052875 A1 20010726, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR,

212th ACS National Meeting, Orlando, FL, August 25-29, CARB-050. American Chemical Society: Washington, D. C. (English) 1996. CODEN: 63BFAF.

AB We describe and compare several routes for the synthesis of the glycopeptide hormone catfish somatostatin (somatostatin-22). The sequence is H-Asp-Asn-Thr-Val-Thr*-Ser-Lys-Pro-Leu-Asn-Cys-Met-Asn-Tyr-Phe-Trp-Lys-Ser-Arg-Thr-Ala-Cys-OH with a cyclic disulfide connecting the two Cys residues. The major "glycoform" of somatostatin-22 carries D-GalNAc and D-Gal O-glycosidically linked to Thr-5 (see *). A minor variant has an addnl. sialic acid attached. The linear sequence was assembled smoothly on supports, using stepwise Fmoc solid-phase chem. Side-chain protection of Cys was provided by S-trityl (Trt). Two glycosylated forms of somatostatin-22 were prepd., using N.alpha.-Fmoc-Thr(Ac3-.alpha.-D-GalNAc)-OH and N.alpha.-Fmoc-Thr(Ac4-.beta.-D-Gal-(1-3)-Ac2-.alpha.-D-GalNAc)-OH. Acidolytic cleavage/deprotection of these peptidyl-resins with TFA-based cocktails gave the corresponding acetyl-protected glycopeptides with free sulhydryls. After de-acetylation with MeOH in the presence of sodium methoxide, the linear glycopeptides were oxidized successfully at pH 7 in the presence of N.alpha.-dithiasuccinoyl (Dts)-glycine, providing the **monomeric cyclic peptides.**

L8 ANSWER 17 OF 28 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 12

94:508181 The Genuine Article (R) Number: PB222. CRYSTAL-STRUCTURE, ELECTROSPRAY-IONIZATION MASS-SPECTROMETRY, ELECTRON-PARAMAGNETIC-RESONANCE, AND MAGNETIC-SUSCEPTIBILITY STUDY OF [CU2(ASCIDH2)(1,2-MU-CO3)(H2O)2]CENTER-DOT-2H2O, THE BIS(COPPER(II)) COMPLEX OF ASCIDIACYCLAMIDE (ASCIDH4), A **CYCLIC PEPTIDE** ISOLATED FROM THE ASCIDIAN LISSOCLINUM-PATELLA. VANDENBRENK A L; BYRIEL K A; FAIRLIE D P; GAHAN L R (Reprint); HANSON G R; HAWKINS C J; JONES A; KENNARD C H L; MOUBARAKI B; MURRAY K S. UNIV QUEENSLAND, DEPT CHEM, BRISBANE, QLD 4072, AUSTRALIA (Reprint); UNIV QUEENSLAND, DEPT CHEM, BRISBANE, QLD 4072, AUSTRALIA; MONASH UNIV, DEPT CHEM, CLAYTON, VIC 3168, AUSTRALIA; UNIV QUEENSLAND, CTR 3D, BRISBANE, QLD 4072, AUSTRALIA; UNIV QUEENSLAND, CTR MAGNET RESONANCE, BRISBANE, QLD 4072, AUSTRALIA. INORGANIC CHEMISTRY (03 AUG 1994) Vol. 33, No. 16, pp. 3549-3557. ISSN: 0020-1669. Pub. country: AUSTRALIA. Language: ENGLISH.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A bis(copper(II)) complex of the naturally occurring **cyclic peptide** ascidiacyclamide (ascidH-4), isolated from the ascidian Lissoclinum patella, has been characterized by X-ray crystallography, magnetic susceptibility measurements, ion spray mass spectrometry, and EPR spectroscopy. The crystals are triclinic, space group P1, with a = 9.9420(10), angstrom, b = 11.808(2), angstrom, c = 20.635(3) angstrom, alpha = 74.340(10)-degrees, beta = 87.520(10)-degrees, gamma = 89.460(10)-degrees, V = 2330.3(6) angstrom3, Z = 2, and R = 0.058. The geometry around one copper(II) atom is distorted square pyramidal, the metal ion coordinated by three nitrogen donors, one each from an oxazoline, a thiazole, and a deprotonated amide. A water molecule and the oxygen atom of a bridging carbonate anion complete the coordination sphere. The other copper(II) atom exhibits a similar coordination environment with an added distant Cu-O interaction making up a distorted octahedral environment. The Cu(I) ... Cu(2) distance was determined as 4.43 angstrom. The geometry of the carbonate anion was considerably distorted from that in the free anion. The presence of the CO32- species was confirmed with ion spray mass spectral studies by comparing the mass spectra of isolated [Cu2(ascidH2)(1,2-mu-CO3)(H2O)2].2H2O with that generated in situ using (CO32-)-C-13 ([ascidH-2 + 2Cu2+ + CO32- + Na+]+: (CO32-)-C-12, m/z 965.2; (CO32-)-C-13, m/z 966.3). Magnetic susceptibility measurements (4-300 K) on the powdered sample show that weak ferromagnetic coupling (2J = +1.6 +/- 0.4 cm-1) occurs, probably via an intramolecular superexchange pathway across the 1,2-mu-CO32- bridge. EPR spectroscopy suggests a structural reorganization of the binuclear copper site when the binuclear copper ascidiacyclamide complex is dissolved in methanol and that the formation of [CU2(ascidH2)(1,2-mu-CO3)(solvent)2] is complicated

by a series of equilibria in which other binuclear and **monomeric** species are involved.

L8 ANSWER 18 OF 28 SCISEARCH COPYRIGHT 2002 ISI (R)
92:104734 The Genuine Article (R) Number: HD008. ONE-POT SYNTHESIS OF OPTICALLY-ACTIVE CYANOHYDRIN ACETATES FROM ALDEHYDES VIA QUINIDINE-CATALYZED TRANSHYDROCYANATION COUPLED WITH LIPASE-CATALYZED KINETIC RESOLUTION IN ORGANIC-SOLVENT. INAGAKI M; HATANAKA A; MIMURA M; HIRATAKE J; NISHIOKA T; ODA J (Reprint). KYOTO UNIV, INST CHEM RES, UJI, KYOTO 611, JAPAN; KAKEN PHARMACEUT CO LTD, DEPT CHEM, CENT RES LABS, KYOTO 607, JAPAN. BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN (JAN 1992) Vol. 65, No. 1, pp. 111-120. ISSN: 0009-2673. Pub. country: JAPAN. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB A novel one-pot synthetic method was developed for the preparation of optically active cyanohydrin acetates. Racemic cyanohydrins were generated from aldehydes and acetone cyanohydrin by quinidine-catalyzed transhydrocyanation, and the resulting cyanohydrins 2a-j were then acetylated by lipase in a stereoselective manner using isopropenyl acetate as an acylating regent. A variety of aldehydes 1a-j were successfully transformed into the corresponding cyanohydrin acetates 3a-j having 47-95% e.e. without isolating the unstable cyanohydrins 2. Moreover, the reversible nature of base-catalyzed transhydrocyanation allows for in situ racemization of the unreacted cyanohydrins and concurrent kinetic resolution by lipase enabled the preparation of (S)-3b-d with 40-82% e.e. in more than 50% yield. Polymer-supported cinchona alkaloid was also used as a catalyst for this one-pot reaction and showed the comparable chemical and optical yield to that for the soluble **monomeric** alkaloid. The insoluble polymer and lipase were recovered by filtration and found to have almost the same catalytic activity even after four times of reuse.

L8 ANSWER 19 OF 28 MEDLINE DUPLICATE 13
92082876 Document Number: 92082876. PubMed ID: 1747407. [Analysis of the structure of prolactin terminal fragments as potential substrates of serine and proline-specific proteinases]. Analiz stroeniia kontsevykh fragmentov prolaktina kak potentsial'nykh substratov serinovykh i prolin-spetsificheskikh proteinaz. Marinchenko G V. BIOKHIMIIA, (1991 May) 56 (5) 771-8. Journal code: 0372667. ISSN: 0320-9725. Pub. country: USSR. Language: Russian.
AB The biochemical mechanism of action of prolactin is unknown. This hormone enters the blood stream and binds to receptors predominantly in the **monomeric** form. A structural analysis of mammalian and piscine prolactin based on the present-day concepts of proteolytic processing of the hormone molecules in target tissues has been carried out. The experimental data suggest that prolactin molecules are protected from exopeptidase influence by their terminal **cyclic peptides**. The highly conservative proline-2 residues increase the resistance of the mammalian hormone N-terminal fragment to the effects of many aminopeptidases. Structurally the C-terminal **cyclic peptides** of prolactin, growth hormone and placental lactogen were shown to be homologous to peptides inhibiting trypsin-like proteinases. A structural analysis of the N-terminal domain of mammalian prolactin revealed the important role of Pro-2 and Pro-4 residues at positions adjacent with and inside the disulfide moiety. It is assumed that these proline residues and the cyclic structure are necessary for the manifestation of the inhibiting effect of the mammalian prolactin N-terminal dodecapeptide on proline-specific proteinases. It is assumed that proteolytic degradation of prolactin molecules in target tissues may induce the secretion of functionally active peptides.

L8 ANSWER 20 OF 28 MEDLINE DUPLICATE 14
92122262 Document Number: 92122262. PubMed ID: 1770501. Association of microcystin-LR and its biotransformation product with a hepatic-cytosolic

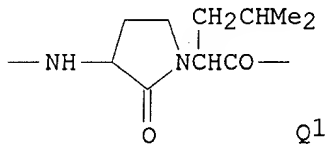
protein. Robinson N A; Matson C F; Pace J G. (Pathophysiology Division, United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland 21702-5011.) JOURNAL OF BIOCHEMICAL TOXICOLOGY, (1991 Fall) 6 (3) 171-80. Journal code: 8700114. ISSN: 0887-2082. Pub. country: United States. Language: English.

AB Microcystin-LR (MCYST-LR), a **cyclic peptide** hepatotoxin, associates with high-molecular-weight, liver cytosolic components. Repetitive cycles of heat denaturation and pronase digestion released 80 +/- 6% of the bound radiolabel from these components, parent toxin (22%), and two biotransformation products, with high-performance liquid chromatography (HPLC) retention times of 6.7 (52%) and 5.6 (13%) min. Both parent and the biotransformed (6.7 min) toxin appeared to be covalently bound to a **monomeric** protein of molecular weight 40,000 (protein plus radiolabeled toxin). Binding and biotransformation reactions were time- and temperature-dependent and did not require endogenous molecules less than 6,000 daltons. The binding appeared to be saturable with a maximum of 20 pmol MCYST-LR bound per mg protein. The binding protein(s) and biotransformation activity were present in rat liver, brain, kidney, heart, lung, small intestine, large intestine, testes, skeletal muscle, and to a lesser extent, in fat. Okadaic acid, a specific protein phosphatase inhibitor, showed a concentration-dependent inhibition of [3H]MCYST-LR binding to hepatic cytosol. The molecular weight and organ distribution of the binding protein(s), and inhibition of binding by okadaic acid were consistent with one of the binding sites being the catalytic subunit of protein phosphatase type 2A.

L8 ANSWER 21 OF 28 CAPLUS COPYRIGHT 2002 ACS

1990:235848 Document No. 112:235848 Preparation of peptides as tachykinin antagonists and pharmaceutical compositions containing them. Curtis, Neil R.; Williams, Brian J. (Merck Sharp and Dohme Ltd., UK). Brit. UK Pat. Appl. GB 2216529 A1 19891011, 32 pp. (English). CODEN: BAXXDU. APPLICATION: GB 1989-5977 19890315. PRIORITY: GB 1988-7246 19880325.

GI



Q1

AB R1(A-Met-XGln-Y-Q-Z)n-R2 (I; A = Leu; X = Gly, bond; Y = arom. amino acid residue; Q = hydrophobic amino acid residue; Z = Gly; n = 1, 2; R1 = amino blocking group; R2 = carboxy blocking group; or R1R2 = bond between the groups Z and A; or ZA optionally together with the bond R1R2 can form moiety Q1) and their N-methylated deriv., useful as tachykinin antagonists, were prepd., e.g., via solid-phase peptide coupling of the appropriate amino acids, cleavage of the peptide chain from the resin with H2NNH2, and coupling of the resulting peptide hydrazide with a 2nd **monomeric** peptide chain. FMOC-Met-NH2 (FMOC = fluorenylmethoxycarbonyl), linked to a resin through an alanine moiety, was sequentially coupled with BOC-(R)-Q1-OH (BOC = Me3CO2C) FMOC-Phe-OH, FMOC-Trp-OH, and BOC-Gln-ONp (Np = p-nitrophenyl) followed by cleavage of the resin with 5% H2NNH2.H2O in MeOH to give BOC-Gln-Trp-Phe-(R)-Q1-Met-NHNH2, which was deprotected with F3CCO2H and cyclized to give cyclo[Gln-Trp-Phe-(R)-Q1-Met]. In an in vitro study, all 11 prepd. I showed inhibition of eledoisin, which was used as a std. agonist of tachykinins. An injectable suspension was prepd. contg. cyclo(Gln-Trp-Phe-Gly-Leu-Met).

L8 ANSWER 22 OF 28 MEDLINE DUPLICATE 15

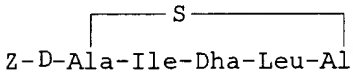
90033032 Document Number: 90033032. PubMed ID: 2806414. Rapid microfilament reorganization induced in isolated rat hepatocytes by microcystin-LR, a **cyclic peptide** toxin. Eriksson J E; Paatero G I; Meriluoto J A; Codd G A; Kass G E; Nicotera P; Orrenius S. (Department of Biology, Abo Akademi University, Turku, Finland.) EXPERIMENTAL CELL RESEARCH, (1989 Nov) 185 (1) 86-100. Journal code: 0373226. ISSN: 0014-4827. Pub. country: United States. Language: English.

AB The cyclic heptapeptide hepatotoxin microcystin-LR from the cyanobacterium Microcystis aeruginosa induces rapid and characteristic deformation of isolated rat hepatocytes. We investigated the mechanism(s) responsible for cell shape changes (blebbing). Our results show that the onset of blebbing was accompanied neither by alteration in intracellular thiol and Ca2+ homeostasis nor by ATP depletion. The irreversible effects were insensitive to protease and phospholipase inhibitors and also to thiol-reducing agents, excluding the involvement of enhanced proteolysis, phospholipid hydrolysis, and thiol modification in microcystin-induced blebbing. In contrast, the cell shape changes were associated with a remarkable reorganization of microfilaments as visualized both by electron microscopy and by fluorescent staining of actin with rhodamine-conjugated phalloidin. The morphological effects and the microfilament reorganization were specific for microcystin-LR and could not be induced by the microfilament-modifying drugs cytochalasin D or phalloidin. Using inhibition of deoxyribonuclease I as an assay for **monomeric** actin, we found that the microcystin-induced reorganization of hepatocyte microfilaments was not due to actin polymerization. On the basis of the rapid microfilament reorganization and the specificity of the effects, it is suggested that microcystin-LR constitutes a novel microfilament-perturbing drug with features that are clearly different from those of cytochalasin D and phalloidin.

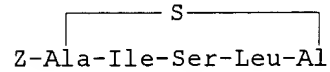
L8 ANSWER 23 OF 28 CAPLUS COPYRIGHT 2002 ACS

1981:16070 Document No. 94:16070 Lanthionine chemistry. Part 5. Synthesis of cyclic nonsymmetrical lanthionyl peptides. Photaki, Iphigenia; Caranikas, Stephanos; Samouilidis, Ioannis; Zervas, Leonidas (Lab. Org. Chem., Univ. Athens, Athens, 144, Greece). J. Chem. Soc., Perkin Trans. 1 (9), 1965-70 (English) 1980. CODEN: JCPRB4. ISSN: 0300-922X.

GI



I



II

AB A protected fragment of the antibiotic nisin, cyclopeptide I (Z = PhCH2O2C, Dha = dehydroalanine residue), and analog II were prepd. Unsym. substituted derivs. of L- or meso-lanthionine were used in the above synthesis. The **monomeric** structures of I and II were proven by mol. wt. detn., and the amino-acrylic acid grouping in I was detd. by amino acid anal. and its IR spectrum.

L8 ANSWER 24 OF 28 CAPLUS COPYRIGHT 2002 ACS

1977:485216 Document No. 87:85216 Studies of the conformation and self-assocation of cyclic decapeptides by triplet-triplet energy transfer. Beyer, C. F.; Craig, L. C.; Gibbons, W. A.; Longworth, J. W. (Rockefeller Univ., New York, N. Y., USA). Excited States Biol. Mol., Proc. Int. Conf., Meeting Date 1974, 411-24. Editor(s): Birks, John B. Wiley: Chichester, Engl. (English) 1976. CODEN: 35CQAY.

GI For diagram(s), see printed CA Issue.

AB The conformations of tyrocidines were detd. from the intramol. and intermol. triplet-triplet energy transfer from ionized tyrosine residues to tryptophan residues. No triplet energy transfer was obsd. in **monomeric** tyrocidine B (I); consequently, the secondary structure does not have these chromophoric residues in close proximity. A flat, antiparallel .beta.-structure for the peptide backbone of I is consistent with previously reported NMR data for tyrocidine A (II). **Monomeric** tyrocidine C (III) has extensive triplet transfer between tyrosine and tryptophan which requires that these residues are sepd. by .apprx.8 .ANG.. This distance may be accommodated to the .beta.-structure by rotating the chromophores about their C.alpha.-C.alpha. bonds to bring them close together.

L8 ANSWER 25 OF 28 CAPLUS COPYRIGHT 2002 ACS

1976:31465 Document No. 84:31465 Peptides. 99. **Monomeric** cyclic cystine peptide derivatives. III. Synthesis of sheep insulin A-chain sequences A2-21 and A1-21 as **monomeric** cyclic dicystine peptide derivatives. Berndt, Heinz; Zahn, Helmut (Dtsch. Wollforschungsinst., Aachen, Ger.). Justus Liebigs Ann. Chem. (9), 1601-12 (German) 1975. CODEN: JLACBF.

AB Sheep insulin A-chain sequences A 1-21 and A 2-21 were prepd. as **monomeric** cyclic dicystine peptide derivs. Previous purifn. difficulties due to insoly. in org. solvents were overcome by using intrachain cystine bridges A 6-7 and A 11-20 which made the insulin fragments sol. in DMF. Protective groups were quant. removed with F3CCO2H and HSCH2CH2OH.

L8 ANSWER 26 OF 28 CAPLUS COPYRIGHT 2002 ACS

1974:459651 Document No. 81:59651 Heterogeneous tryptophan environments in the **cyclic peptides** tyrocidines B and C. Phosphorescence studies. Beyer, Carl F.; Gibbons, William A.; Craig, Lyman C.; Longworth, James W. (Rockefeller Univ., New York, N. Y., USA). J. Biol. Chem., 249(10), 3204-11 (English) 1974. CODEN: JBCHA3.

AB Phosphorescence spectroscopy was used to probe the microenvironments of the tryptophan [73-22-3] residues of the cyclic antibiotic decapeptides tyrocidine B [865-28-1] (which contains 1 tryptophan residue) and tyrocidine C [3252-29-7] (which contains 2 tryptophan residues). Both peptides exhibited 2 distinct, overlapping tryptophan phosphorescence emission spectra under appropriate solvent conditions. The 2 emissions had characteristically different wavelength positions, phosphorescence lifetimes, and excitation spectra, and their relative intensities were strongly solvent-dependent. An open chain deriv. of tyrocidine B, which has no biol. activity, showed only a single phosphorescence emission from tryptophan. This indicated that the environmental heterogeneity of tryptophan residues in the intact peptides arose not from their primary structures but from higher structural features. Factors which are known to increase the self-assocn. of the tyrocidines, such as higher peptide concns. or greater amts. of H2O in alc.-H2O solvent mixts., generally led to enhanced emission of the lower energy phosphorescence component relative to the higher energy one. Thus, the higher energy component of the phosphorescence emission comes from solvent-exposed tryptophan residues of **monomeric** peptide mols., and the lower energy component from tryptophan residues buried in the hydrophobic interior of peptide aggregates. These **cyclic peptides** reveal many of the phosphorescence complexities obsd. with native proteins and thus are useful as model compds. in correlating tryptophan microenvironments with emission characteristics.

L8 ANSWER 27 OF 28 CAPLUS COPYRIGHT 2002 ACS

1975:58105 Document No. 82:58105 Reduction-reoxidation studies with crosslinked insulin derivatives. Wollmer, Axel; Brandenburg, Dietrich; Vogt, Hans P.; Schermutzki, Winrich (Abt. Physiol. Chem., Rheinisch-Westfael. Tech. Hochsch. Aachen, Aachen, Ger.). Hoppe-Seyler's

Z. Physiol. Chem., 355(11), 1471-6 (English) 1974. CODEN: HSZPAZ.
AB Reoxidn. of reduced N.alpha.A1-N.epsilon.B29 crosslinked oxalyl-, adipoyl-, suberoyl-, and tridecanedioylinsulins of bovines at pH 8.5-9.0 and 0.1 mg protein/ml yielded 48-74% products which were identical with the authentic derivs. as judged from CD spectra and their changes on addn. of Zn2+. Reoxidn. in 7M urea did not lead to the original conformation. With N.alpha.A1-N.alpha.B1-suberoylinsulin only 26% **monomeric** reoxidn. products were obtained which were significantly different from the authentic material and which were similar to the one obtained when the reoxidn. was carried out in 7M urea. The major change towards the CD spectrum of the authentic material occurred between 2 and 4 hr, i.e. when the backformation of disulfide bridges increased from 2 to 4.

L8 ANSWER 28 OF 28 CAPLUS COPYRIGHT 2002 ACS
1951:41711 Document No. 45:41711 Original Reference No. 45:7171c-e Size, shape, and aggregation of tropomyosin particles. Tsao, T. C.; Bailey, K.; Adair, G. S. (Univ. Cambridge, UK). Biochem. J., 49, 27-36 (Unavailable) 1951.
AB Studies on rabbit tropomyosin show that the av. particle wt. in salt solns. of pH 6.5 falls as the ionic strength of the solute increases. The value approaches 53,000 found under depolymerization with 6.7 M urea. The same particle size is obtained at pH 2, while in the alk. medium of pH 12 somewhat higher values are found (61,000). The tropomyosin recovered from salt solns., acid, and alkali behaves like the original material. It can be stored for weeks at 0.degree. at pH 2 or 12 without evidence of a splitting of peptide bonds, and the tropomyosin can be crystd. However, after treatment with urea it no longer crystallizes and tends to form fibrils. From viscometric studies it is concluded that structural factors rather than orientation det. certain phenomena. The tropomyosin consisting of a **cyclic peptide** chain has a particle wt. of 53,000 in the **monomeric** form, and the asymmetry of an extended loop can be calcd. from viscosity data which indicate a length of 385 A., mean width 14.5 A., and an axial ratio of 25.

=> s (achen m?/au or hughes r?/au or stacker s?/au or cendron a?/au)
L9 9964 (ACHEN M?/AU OR HUGHES R?/AU OR STACKER S?/AU OR CENDRON A?/AU)

=> s l9 and VEGF-D
L10 67 L9 AND VEGF-D

=> s l10 and cyclic peptide
L11 1 L10 AND CYCLIC PEPTIDE

=> d l11 cbib abs

L11 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:545508 Document No. 135:132464 **Cyclic peptide** inhibitors of VEGF, VEGF-C, and **VEGF-D**, preparation methods, pharmaceutical compositions, and therapeutic use. **Achen, Marc G.; Hughes, Richard A.; Stacker, Steven; Cendron, Angela** (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001052875 A1 20010726, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1533 20010118. PRIORITY: US 2000-PV176293 20000118; US 2000-PV204590 20000516.
AB The invention provides monomeric monocyclic peptide inhibitors and dimeric

bicyclic peptide inhibitors based on exposed loop fragments of a growth factor protein, e.g. loop 1, loop 2 or loop 3 of **VEGF-D** , as well as methods of making them, pharmaceutical compns. contg. them, and therapeutic methods of use.

=> dup remove l10
PROCESSING COMPLETED FOR L10
L12 22 DUP REMOVE L10 (45 DUPLICATES REMOVED)

=> d l12 1-22 cbib abs

L12 ANSWER 1 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2002:334517 Document No.: PREV200200334517. Antibodies to truncated **VEGF-D** and thereof. **Achen, Marc G. (1); Stacker, Steven Alan.** (1) Parkville Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6383484 May 07, 2002. Official Gazette of the United States Patent and Trademark Office Patents, (May 7, 2002) Vol. 1258, No. 1, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133. Language: English.

AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated **VEGF-D**. One of these antibodies can interfere with the activity of **VEGF-D** mediated by VEGFR-2 and interfere with the binding of **VEGF-D** to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L12 ANSWER 2 OF 22 MEDLINE
2002296322 Document Number: 22032677. PubMed ID: 12036873. Adenovirus encoding vascular endothelial growth factor-D induces tissue-specific vascular patterns in vivo. Byzova Tatiana V; Goldman Corey K; Jankau Jurek; Chen Juhua; Cabrera Gustavo; **Achen Marc G; Stacker Steven A;** Carnevale Kevin A; Siemionow Maria; Deitcher Steven R; DiCorleto Paul E. (Departments of Molecular Cardiology and Cardiology, Vascular Medicine, Cell Biology, and Plastic and Reconstructive Surgery, The Cleveland Clinic Foundation, OH; and the Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.) BLOOD, (2002 Jun 15) 99 (12) 4434-42. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB The capacity of an adenovirus encoding the mature form of vascular endothelial growth factor (**VEGF**)-**D**, VEGF-DDeltaNDeltaC, to induce angiogenesis, lymphangiogenesis, or both was analyzed in 2 distinct in vivo models. We first demonstrated in vitro that VEGF-DDeltaNDeltaC encoded by the adenovirus (Ad-VEGF-DDeltaNDeltaC) is capable of inducing endothelial cell proliferation and migration and that the latter response is primarily mediated by VEGF receptor-2 (VEGFR-2). Second, we characterized a new in vivo model for assessing experimental angiogenesis, the rat cremaster muscle, which permits live videomicroscopy and quantitation of functional blood vessels. In this model, a proangiogenic effect of Ad-VEGF-DDeltaNDeltaC was evident as early as 5 days after injection. Immunohistochemical analysis of the cremaster muscle demonstrated that neovascularization induced by Ad-VEGF-DDeltaNDeltaC and by Ad-VEGF-A(165) (an adenovirus encoding the 165 isoform of VEGF-A) was composed primarily of laminin and VEGFR-2-positive vessels containing red blood cells, thus indicating a predominantly angiogenic response. In a skin model, Ad-VEGF-DDeltaNDeltaC induced angiogenesis and lymphangiogenesis, as indicated by staining with laminin, VEGFR-2, and VEGFR-3, whereas Ad-VEGF-A(165) stimulated the selective growth of blood vessels. These data suggest that the biologic effects of **VEGF-D** are tissue-specific and dependent on the abundance of blood

vessels and lymphatics expressing the receptors for **VEGF-D** in a given tissue. The capacity of Ad-VEGF-DDeltaNDeltaC to induce endothelial cell proliferation, angiogenesis, and lymphangiogenesis demonstrates that its potential usefulness for the treatment of coronary artery disease, cerebral ischemia, peripheral vascular disease, restenosis, and tissue edema should be tested in preclinical models. (Blood. 2002;99:4434-4442)

L12 ANSWER 3 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2001:534079 Document No.: PREV200100534079. Vascular endothelial growth factor-D (**VEGF-D**) polypeptides. **Achen, Marc G.** **(1)**; Wilks, Andrew F.; **Stacker, Steven A.**; Alitalo, Kari. (1) Fitzroy Australia. ASSIGNEE: Ludwig Institute for Cancer Research; Helsinki University Licensing Ltd., Helsinki, Finland. Patent Info.: US 6235713 May 22, 2001. Official Gazette of the United States Patent and Trademark Office Patents, (May 22, 2001) Vol. 1246, No. 4, pp. No Pagination. e-file. ISSN: 0098-1133. Language: English.

AB **VEGF-D**, a new member of the PDGF family of growth factors, which among other things stimulates endothelial cell proliferation and angiogenesis and increases vascular permeability, as well as nucleotide sequences encoding it, methods for producing it, antibodies and other antagonists to it, transfected or transformed host cells for expressing it, pharmaceutical compositions containing it, and uses thereof in medical and diagnostic applications.

L12 ANSWER 4 OF 22 CAPLUS COPYRIGHT 2002 ACS
2001:661270 Document No. 135:205534 Methods for treating, screening for, and detecting cancers expressing vascular endothelial growth factor D (**VEGF-D**). **Achen, Marc; Stacker, Steven** (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001064235 A1 20010907, 78 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US6791 20010302. PRIORITY: US 2000-PV186361 20000302.

AB A method for treating and alleviating melanomas and various cancers characterized by the expression of **VEGF-D** by the tumor comprises screening to find an organism with tumor cells expressing **VEGF-D** and administering an effective amt. of a **VEGF-D** antagonist to prevent binding of **VEGF-D**. Also provided are methods for screening for neoplastic diseases, where detection of **VEGF-D** on or in cells such as tumor cells, blood vessel endothelial cells, lymph vessel endothelial cells, and/or cells with potential neoplastic growth indicates neoplastic disease; a method for promoting and maintaining vascularization of normal tissue in an organism by administering **VEGF-D** or a fragment or analog thereof; methods for screening tumors for metastatic risk where expression of **VEGF-D** by the tumor indicates metastatic risk; and methods to detect micro-metastasis of neoplastic disease where detection of **VEGF-D** on or in a tissue sample indicates metastasis of neoplastic disease.

L12 ANSWER 5 OF 22 CAPLUS COPYRIGHT 2002 ACS
2001:545508 Document No. 135:132464 Cyclic peptide inhibitors of VEGF, VEGF-C, and **VEGF-D**, preparation methods, pharmaceutical compositions, and therapeutic use. **Achen, Marc G.**; **Hughes, Richard A.**; **Stacker, Steven**; **Cendron, Angela** (Ludwig Institute for Cancer Research, USA). PCT Int. Appl.

WO 2001052875 A1 20010726, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1533 20010118. PRIORITY: US 2000-PV176293 20000118; US 2000-PV204590 20000516.

AB The invention provides monomeric monocyclic peptide inhibitors and dimeric bicyclic peptide inhibitors based on exposed loop fragments of a growth factor protein, e.g. loop 1, loop 2 or loop 3 of **VEGF-D**, as well as methods of making them, pharmaceutical compns. contg. them, and therapeutic methods of use.

L12 ANSWER 6 OF 22 MEDLINE DUPLICATE 1

2001679531 Document Number: 21570255. PubMed ID: 11574540. Multiple forms of mouse vascular endothelial growth factor-D are generated by RNA splicing and proteolysis. Baldwin M E; Roufail S; Halford M M; Alitalo K; **Stacker S A; Achen M G.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Post Office Box 2008, Victoria 3050, Australia.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Nov 23) 276 (47) 44307-14. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The secreted glycoprotein vascular endothelial growth factor-D (**VEGF-D**) is angiogenic, lymphangiogenic, and promotes metastatic spread of tumor cells via lymphatic vessels. **VEGF-D** consists of a receptor-binding domain (VEGF homology domain) and N- and C-terminal propeptides. Proteolytic processing produces numerous forms of human **VEGF-D**, including fully processed derivatives (containing only the VEGF homology domain), partially processed, and unprocessed derivatives. Proteolysis is essential to generate human **VEGF-D** that binds the angiogenic receptor VEGF receptor-2 (VEGFR-2) and the lymphangiogenic receptor VEGFR-3 with high affinity. Here, we report that alternative use of an RNA splice donor site in exon 6 of the mouse **VEGF-D** gene produces two different protein isoforms, **VEGF-D**(358) and **VEGF-D**(326), with distinct C termini. The two isoforms were both expressed in all adult mouse tissues and embryonic stages of development analyzed. Both isoforms are proteolytically processed in a similar fashion to human **VEGF-D** to generate a range of secreted derivatives and bind and cross-link VEGFR-3 with similar potency. The isoforms are differently glycosylated when expressed in vitro. This study demonstrates that RNA splicing, protein glycosylation, and proteolysis are mechanisms for generating structural diversity of mouse **VEGF-D**.

L12 ANSWER 7 OF 22 MEDLINE DUPLICATE 2

2001328395 Document Number: 21276411. PubMed ID: 11279005. The specificity of receptor binding by vascular endothelial growth factor-d is different in mouse and man. Baldwin M E; Catimel B; Nice E C; Roufail S; Hall N E; Stenvers K L; Karkkainen M J; Alitalo K; **Stacker S A; Achen M G.** (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050 Australia.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jun 1) 276 (22) 19166-71. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Human vascular endothelial growth factor-D (**VEGF-D**) binds and activates VEGFR-2 and VEGFR-3, receptors expressed on vascular and lymphatic endothelial cells. As VEGFR-2 signals for angiogenesis and VEGFR-3 is thought to signal for lymphangiogenesis, it was proposed that **VEGF-D** stimulates growth of blood vessels and lymphatic vessels into regions of embryos and tumors. Here we report the unexpected

finding that mouse **VEGF-D** fails to bind mouse VEGFR-2 but binds and cross-links VEGFR-3 as demonstrated by biosensor analysis with immobilized receptor domains and bioassays of VEGFR-2 and VEGFR-3 cross-linking. Mutation of amino acids in mouse **VEGF-D** to those in the human homologue indicated that residues important for the VEGFR-2 interaction are clustered at, or are near, the predicted receptor-binding surface. Coordinated expression of **VEGF-D** and VEGFR-3 in mouse embryos was detected in the developing skin where the **VEGF-D** gene was expressed in a layer of cells beneath the developing epidermis and VEGFR-3 was localized on a network of vessels immediately beneath the **VEGF-D** -positive cells. This suggests that **VEGF-D** and VEGFR-3 may play a role in establishing vessels of the skin by a paracrine mechanism. Our study of receptor specificity suggests that **VEGF-D** may have different biological functions in mouse and man.

L12 ANSWER 8 OF 22 MEDLINE DUPLICATE 3

2001509463 Document Number: 21423456. PubMed ID: 11532940. Isolated lymphatic endothelial cells transduce growth, survival and migratory signals via the VEGF-C/D receptor VEGFR-3. Makinen T; Veikkola T; Mustjoki S; Karpanen T; Catimel B; Nice E C; Wise L; Mercer A; Kowalski H; Kerjaschki D; **Stacker S A; Achen M G;** Alitalo K. (Molecular/Cancer Biology Laboratory and Ludwig Institute for Cancer Research, and Helsinki University Hospital, Biomedicum Helsinki, University of Helsinki, FIN-00014 Helsinki, Finland.) EMBO JOURNAL, (2001 Sep 3) 20 (17) 4762-73. Journal code: 8208664. ISSN: 0261-4189. Pub. country: England: United Kingdom. Language: English.

AB Vascular endothelial growth factor receptor-3 (VEGFR-3/Flt4) binds two known members of the VEGF ligand family, VEGF-C and **VEGF-D**, and has a critical function in the remodelling of the primary capillary vasculature of midgestation embryos. Later during development, VEGFR-3 regulates the growth and maintenance of the lymphatic vessels. In the present study, we have isolated and cultured stable lineages of blood vascular and lymphatic endothelial cells from human primary microvascular endothelium by using antibodies against the extracellular domain of VEGFR-3. We show that VEGFR-3 stimulation alone protects the lymphatic endothelial cells from serum deprivation-induced apoptosis and induces their growth and migration. At least some of these signals are transduced via a protein kinase C-dependent activation of the p42/p44 MAPK signalling cascade and via a wortmannin-sensitive induction of Akt phosphorylation. These results define the critical role of VEGF-C/VEGFR-3 signalling in the growth and survival of lymphatic endothelial cells. The culture of isolated lymphatic endothelial cells should now allow further studies of the molecular properties of these cells.

L12 ANSWER 9 OF 22 MEDLINE DUPLICATE 4

2001216875 Document Number: 21150098. PubMed ID: 11250889. Signalling via vascular endothelial growth factor receptor-3 is sufficient for lymphangiogenesis in transgenic mice. Veikkola T; Jussila L; Makinen T; Karpanen T; Jeltsch M; Petrova T V; Kubo H; Thurston G; McDonald D M; **Achen M G; Stacker S A;** Alitalo K. (Molecular/Cancer Biology Laboratory and Ludwig Institute for Cancer Research, Haartman Institute, University of Helsinki, PO Box 21 (Haartmaninkatu 3), 00014 Helsinki, Finland.) EMBO JOURNAL, (2001 Mar 15) 20 (6) 1223-31. Journal code: 8208664. ISSN: 0261-4189. Pub. country: England: United Kingdom. Language: English.

AB Vascular endothelial growth factor receptor-3 (VEGFR-3) has an essential role in the development of embryonic blood vessels; however, after midgestation its expression becomes restricted mainly to the developing lymphatic vessels. The VEGFR-3 ligand VEGF-C stimulates lymphangiogenesis in transgenic mice and in chick chorioallantoic membrane. As VEGF-C also binds VEGFR-2, which is expressed in lymphatic endothelia, it is not clear which receptors are responsible for the lymphangiogenic effects of VEGF-C.

VEGF-D, which binds to the same receptors, has been reported to induce angiogenesis, but its lymphangiogenic potential is not known. In order to define the lymphangiogenic signalling pathway we have created transgenic mice overexpressing a VEGFR-3-specific mutant of VEGF-C (VEGF-C156S) or **VEGF-D** in epidermal keratinocytes under the keratin 14 promoter. Both transgenes induced the growth of lymphatic vessels in the skin, whereas the blood vessel architecture was not affected. Evidence was also obtained that these growth factors act in a paracrine manner in vivo. These results demonstrate that stimulation of the VEGFR-3 signal transduction pathway is sufficient to induce specifically lymphangiogenesis in vivo.

L12 ANSWER 10 OF 22 MEDLINE DUPLICATE 5
2002052394 Document Number: 21636910. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Debinski W; Slagle-Webb B; **Achen M G**; **Stacker S A**; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . MOLECULAR MEDICINE, (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervascularized and locally infiltrating brain tumor of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (**VEGF-D**), is the newest mammalian member of VEGF family. We analyzed **VEGF-D** in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of **VEGF-D**, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously **VEGF-D**, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced **VEGF-D** expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and **VEGF-D** levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because **VEGF-D** activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The **VEGF-D** system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

L12 ANSWER 11 OF 22 MEDLINE DUPLICATE 6
2001212643 Document Number: 21110004. PubMed ID: 11175849. **VEGF-D** promotes the metastatic spread of tumor cells via the lymphatics. **Stacker S A**; Caesar C; Baldwin M E; Thornton G E; Williams R A; Prevo R; Jackson D G; Nishikawa S; Kubo H; **Achen M G** . (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.) NATURE MEDICINE, (2001 Feb) 7 (2) 186-91. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Metastasis to local lymph nodes via the lymphatic vessels is a common step in the spread of solid tumors. To investigate the molecular mechanisms underlying the spread of cancer by the lymphatics, we examined the ability

of vascular endothelial growth factor (**VEGF**)-**D**, a ligand for the lymphatic growth factor receptor VEGFR-3/Flt-4, to induce formation of lymphatics in a mouse tumor model. Staining with markers specific for lymphatic endothelium demonstrated that **VEGF-D** induced the formation of lymphatics within tumors. Moreover, expression of **VEGF-D** in tumor cells led to spread of the tumor to lymph nodes, whereas expression of VEGF, an angiogenic growth factor which activates VEGFR-2 but not VEGFR-3, did not. **VEGF-D** also promoted tumor angiogenesis and growth. Lymphatic spread induced by **VEGF-D** could be blocked with an antibody specific for **VEGF-D**. This study demonstrates that lymphatics can be established in solid tumors and implicates VEGF family members in determining the route of metastatic spread.

L12 ANSWER 12 OF 22 MEDLINE DUPLICATE 7

2001156199 Document Number: 21104372. PubMed ID: 11180159. Localization of vascular endothelial growth factor-D in malignant melanoma suggests a role in tumour angiogenesis. **Achen M G**; Williams R A; Minekus M P; Thornton G E; Stenvers K; Rogers P A; Lederman F; Roufail S; **Stacker S A**. (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050, Australia.. Marc.achen@ludwig.edu.au) . JOURNAL OF PATHOLOGY, (2001 Feb) 193 (2) 147-54. Journal code: 0204634. ISSN: 0022-3417. Pub. country: England: United Kingdom. Language: English.

AB Expression of angiogenic and lymphangiogenic factors by tumours may influence the route of metastatic spread. Vascular endothelial growth factor (VEGF) is a regulator of tumour angiogenesis, but studies of the inhibition of solid tumour growth by neutralizing anti-VEGF antibodies indicated that other angiogenic factors may be involved. **VEGF-D** may be an alternative regulator because like VEGF it is angiogenic and it activates VEGF receptor-2 (VEGFR-2), an endothelial cell receptor which is a key signalling molecule in tumour angiogenesis. This study reports the generation of monoclonal antibodies to the receptor-binding domain of **VEGF-D** and the use of these antibodies to localize **VEGF-D** in malignant melanoma. **VEGF-D** was detected in tumour cells and in vessels adjacent to immunopositive tumour cells, but not in vessels distant from the tumours. These findings are consistent with a model in which **VEGF-D**, secreted by tumour cells, activates endothelial cell receptors and thereby contributes to the regulation of tumour angiogenesis and possibly lymphangiogenesis. In addition, **VEGF-D** was detected in the vascular smooth muscle, but not the endothelium, of vessels in adult colon. The endothelium of these vessels was negative for VEGFR-2 and VEGFR-3. As VEGF receptors can be up-regulated on endothelium in response to vessel damage and ischaemia, these findings of a specific localization of **VEGF-D** in smooth muscle of the blood vessels suggest that **VEGF-D** produced by vascular smooth muscle could play a role in vascular repair by stimulating the proliferation of endothelial cells.

L12 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2002 ACS

2000:441581 Document No. 133:72945 Antibodies to truncated **VEGF-D** and uses thereof. **Achen, Marc G.; Stacker, Steven Alan** (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2000037025 A2 20000629, 44 pp. DESIGNATED STATES: W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US31332 19991221. PRIORITY: US 1998-PV113254 19981221; US 1999-PV134556 19990517.

AB The invention is based on the isolation of antibodies that were made to a

polypeptide having the amino acid sequence for a truncated **VEGF-D**. One of these antibodies can interfere with the activity of **VEGF-D** mediated by VEGFR-2 and interfere with the binding of **VEGF-D** to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The antibodies, antibody fragments or compns. contg. the antibodies are useful for diagnosis, prognosis, and therapy of **VEGF-D** or VEGF-C related diseases, e.g. cancer, diabetic retinopathy, psoriasis, arthropathy, fluid accumulation in the heart and/or lung.

L12 ANSWER 14 OF 22 CAPLUS COPYRIGHT 2002 ACS

2000:290851 Document No. 132:318341 Use of VEGF-C or **VEGF-D** gene or protein to prevent restenosis. Yla-Herttuala, Seppo; Alitalo, Kari; Hiltunen, Mikko O.; Jeltsch, Markku M.; **Achen, Marc G.** (Ludwig Institute for Cancer Research, USA; Helsinki University Licensing Ltd. Oy). PCT Int. Appl. WO 2000024412 A2 20000504, 61 pp. DESIGNATED STATES: W: AU, CA, CN, JP, NO, NZ; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US24054 19991026. PRIORITY: US 1998-PV105587 19981026.

AB The present invention provides materials and methods for preventing stenosis or restenosis of a blood vessel using Vascular Endothelial Growth Factor C (VEGF-C) and/or Vascular Endothelial Growth Factor D (**VEGF-D**) genes or proteins. A medical device designed to contact a surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel is also claimed, the device characterized by an improvement comprising integrating into the device a compn. effective to prevent restenosis, said compn. comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide, a VEGF-C polypeptide, a **VEGF-D** polynucleotide, and a **VEGF-D** polypeptide. The medical device is selected from the group consisting of intravascular stents, intravascular catheters, extravascular collars, elastomeric membranes adapted to cover a surface of an intravascular stent or catheter, and combinations thereof. Also claimed is a kit for treating restenosis comprising a container holding at least one anti-restenosis agent of the invention and a label attached to or packaged with the container, the label describing use of the compd. for prevention of restenosis of a blood vessel. The kit further comprises a medical device of the invention.

L12 ANSWER 15 OF 22 MEDLINE DUPLICATE 8

2000247148 Document Number: 20247148. PubMed ID: 10785369. Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. **Achen M G;** Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; **Stacker S A.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . EUROPEAN JOURNAL OF BIOCHEMISTRY, (2000 May) 267 (9) 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (**VEGF-D**), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. **VEGF-D** consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human **VEGF-D** in order to generate **VEGF-D** antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed **VEGF-D**. We demonstrate, using bioassays for the binding and

cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature **VEGF-D** for binding to both VEGFR-2 and VEGFR-3 for binding to mature **VEGF-D**. This indicates that the binding epitopes on **VEGF-D** for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to **VEGF-D**. The anti-(**VEGF-D**) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of **VEGF-D**
.

L12 ANSWER 16 OF 22 MEDLINE DUPLICATE 9
2001021068 Document Number: 20480660. PubMed ID: 11023993. VEGF-C and **VEGF-D** expression in neuroendocrine cells and their receptor, VEGFR-3, in fenestrated blood vessels in human tissues. Partanen T A; Arola J; Saaristo A; Jussila L; Ora A; Miettinen M; **Stacker S A; Achen M G;** Alitalo K. (Molecular/Cancer Biology Laboratory and Department of Pathology, Haartman Institute, University of Helsinki, 00014 Helsinki, Finland.) FASEB JOURNAL, (2000 Oct) 14 (13) 2087-96. Journal code: 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.

AB Recently, vascular endothelial growth factor receptor 3 (VEGFR-3) has been shown to provide a specific marker for lymphatic endothelia in certain human tissues. In this study, we have investigated the expression of VEGFR-3 and its ligands VEGF-C and **VEGF-D** in fetal and adult tissues. VEGFR-3 was consistently detected in the endothelium of lymphatic vessels such as the thoracic duct, but fenestrated capillaries of several organs including the bone marrow, splenic and hepatic sinusoids, kidney glomeruli and endocrine glands also expressed this receptor. VEGF-C and **VEGF-D**, which bind both VEGFR-2 and VEGFR-3 were expressed in vascular smooth muscle cells. In addition, intense cytoplasmic staining for VEGF-C was observed in neuroendocrine cells such as the alpha cells of the islets of Langerhans, prolactin secreting cells of the anterior pituitary, adrenal medullary cells, and dispersed neuroendocrine cells of the gastrointestinal tract. **VEGF-D** was observed in the innermost zone of the adrenal cortex and in certain dispersed neuroendocrine cells. These results suggest that VEGF-C and **VEGF-D** have a paracrine function and perhaps a role in peptide release from secretory granules of certain neuroendocrine cells to surrounding capillaries.

L12 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2002 ACS
2000:773478 Document No. 134:66223 Growth factors regulating lymphatic vessels. Lymboussaki, A.; **Achen, M. G.; Stacker, S. A.** ; Alitalo, K. (Molecular/Cancer Biology Laboratory, Haartman Institute, University of Helsinki, Finland, 00014, Finland). Current Topics in Microbiology and Immunology, 251(Lymphoid Organogenesis), 75-82 (English) 2000. CODEN: CTMIA3. ISSN: 0070-217X. Publisher: Springer-Verlag.

AB A review with 44 refs. Over the past 10 yr, much has been learned about the mol. control of angiogenesis, but only recently have the first regulators of lymphangiogenesis been identified. The availability of VEGF-C and **VEGF-D** offers the opportunity to induce lymphangiogenesis in the clinic, which may be useful for treatment of lymphedema. The expression of VEGF-C and **VEGF-D** in tumors raises the possibility of tumor lymphangiogenesis. Despite involvement of the lymphatics in tumor metastasis, little is known about the relationship between tumor cells and the lymphatic endothelium. The route by which a tumor metastasizes may, in part, be detd. by the angiogenic/lymphangiogenic growth factors secreted by tumor cells that modulate the prevalence of vessels in a tumor. Specific inhibitors of VEGF-C, **VEGF-D** or VEGFR-3 will be required to address this important issue.

L12 ANSWER 18 OF 22 CAPLUS COPYRIGHT 2002 ACS
1999:468435 Document No. 131:83470 Expression vectors and cell lines expressing vascular endothelial growth factor D, and method of treating melanomas. **Achen, Marc G.; Stacker, Steven Alan;** Alitalo, Kari (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 9933485 A1 19990708, 79 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, NZ; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US27373 19981223. PRIORITY: AU 1997-1131 19971224; US 1998-87392 19980529.

AB This invention relates to expression vectors comprising **VEGF-D** and its biol. active derivs., cell lines stably expressing **VEGF-D** and its biol. active derivs., and to a method of making a polypeptide using these expression vectors and host cells. Optionally, **VEGF-D** produced by the cell line of the invention is linked to an epitope tag such as FLAG, hexahistidine, or I-SPY, to facilitate purifn. of the polypeptide by affinity chromatog. The mammalian cell line may preferably be the 293-EBNA human embryonal kidney cell line, and several Apex-3 plasmid expression constructs are provided. The invention also relates to a method for treating and alleviating melanomas or tumors expressing **VEGF-D** and various diseases.

L12 ANSWER 19 OF 22 MEDLINE DUPLICATE 10
2000044745 Document Number: 20044745. PubMed ID: 10574962. A mutant form of vascular endothelial growth factor (VEGF) that lacks VEGF receptor-2 activation retains the ability to induce vascular permeability. **Stacker S A;** Vitali A; Caesar C; Domagala T; Groenen L C; Nice E; **Achen M G;** Wilks A F. (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050 Australia.. Steven.stacker@ludwig.edu.au) . JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Dec 3) 274 (49) 34884-92. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor (VEGF) is a major mediator of vasculogenesis and angiogenesis both during development and in pathological conditions. VEGF has a variety of effects on vascular endothelium, including the ability to stimulate endothelial cell mitogenesis, and the potent induction of vascular permeability. These activities are at least in part mediated by binding to two high affinity receptors, VEGFR-1 and VEGFR-2. In this study we have made mutations of mouse VEGF in order to define the regions that are required for VEGFR-2-mediated functions. Development of a bioassay, which responds only to signals generated by cross-linking of VEGFR-2, has allowed evaluation of these mutants for their ability to activate VEGFR-2. One mutant (VEGF0), which had amino acids 83-89 of VEGF substituted with the analogous region of the related placenta growth factor, demonstrated significantly reduced VEGFR-2 binding compared with wild type VEGF, indicating that this region was required for VEGF-VEGFR-2 interaction. Intriguingly, when this mutant was evaluated in a Miles assay for its ability to induce vascular permeability, no difference was found when compared with wild type VEGF. In addition we have shown that the VEGF homology domain of the structurally related growth factor **VEGF-D** is capable of binding to and activating VEGFR-2 but has no vascular permeability activity, indicating that VEGFR-2 binding does not correlate with permeability activity for all VEGF family members. These data suggest different mechanisms for VEGF-mediated mitogenesis and vascular permeability and raise the possibility of an alternative receptor mediating vascular permeability.

L12 ANSWER 20 OF 22 MEDLINE DUPLICATE 11
2000011413 Document Number: 20011413. PubMed ID: 10542248. Biosynthesis of vascular endothelial growth factor-D involves proteolytic processing which generates non-covalent homodimers. **Stacker S A;** Stenvers

K; Caesar C; Vitali A; Domagala T; Nice E; Roufail S; Simpson R J; Moritz R; Karpanen T; Alitalo K; **Achen M G.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia.. steven.stacker@ludwig.edu.au) . JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Nov 5) 274 (45) 32127-36. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor-D (**VEGF-D**) binds and activates the endothelial cell tyrosine kinase receptors VEGF receptor-2 (VEGFR-2) and VEGF receptor-3 (VEGFR-3), is mitogenic for endothelial cells, and shares structural homology and receptor specificity with VEGF-C. The primary translation product of **VEGF-D** has long N- and C-terminal polypeptide extensions in addition to a central VEGF homology domain (VHD). The VHD of **VEGF-D** is sufficient to bind and activate VEGFR-2 and VEGFR-3. Here we report that **VEGF-D** is proteolytically processed to release the VHD. Studies in 293EBNA cells demonstrated that **VEGF-D** undergoes N- and C-terminal cleavage events to produce numerous secreted polypeptides including a fully processed form of M(r) approximately 21,000 consisting only of the VHD, which is predominantly a non-covalent dimer. Biosensor analysis demonstrated that the VHD has approximately 290- and approximately 40-fold greater affinity for VEGFR-2 and VEGFR-3, respectively, compared with unprocessed **VEGF-D**. In situ hybridization demonstrated that embryonic lung is a major site of expression of the **VEGF-D** gene. Processed forms of **VEGF-D** were detected in embryonic lung indicating that **VEGF-D** is proteolytically processed in vivo.

L12 ANSWER 21 OF 22 CAPLUS COPYRIGHT 2002 ACS

1998:151220 Document No. 128:213742 Vascular endothelial cell growth factor D (**VEGF-D**) and a cDNA encoding and their uses.
Achen, Marc G.; Wilks, Andrew F.; **Stacker, Steven A.**; Alitalo, Kari (Ludwig Institute for Cancer Research, USA; Helsinki University Licensing Ltd., Oy). PCT Int. Appl. WO 9807832 A1 19980226, 101 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US14696 19970821. PRIORITY: AU 1996-1825 19960823; US 1996-23751 19960823; AU 1996-3554 19961111; US 1996-31097 19961114; AU 1997-4954 19970205; US 1997-38814 19970210; AU 1997-7435 19970619; US 1997-51426 19970701.

AB **VEGF-D**, a new member of the PDGF family of growth factors, which among other things stimulates endothelial cell proliferation and angiogenesis and increases vascular permeability, is described. A cDNA encoding it is cloned. Methods for manuf. of **VEGF-D**, antibodies and other antagonists to it, transgenic cells for manuf. of the protein, pharmaceutical compns. contg. it, and its therapeutic and diagnostic uses are also described. An EST clone encoding a novel member of the VEGF family was identified during a database search. This partial sequence was used to probe a human breast cDNA library and a full-length clone obtained. The protein shows amino acid sequence similarities to VEGF-C and to Tie-2 ligand 1. A bioassay was used to demonstrate that **VEGF-D** bound the gene KDR receptor and stimulated endothelial cell proliferation.

L12 ANSWER 22 OF 22 MEDLINE DUPLICATE 12

1998118549 Document Number: 98118549. PubMed ID: 9435229. Vascular endothelial growth factor D (**VEGF-D**) is a ligand for the tyrosine kinases VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4).
Achen M G; Jeltsch M; Kukk E; Makinen T; Vitali A; Wilks A F;

Alitalo K; **Stacker S A**. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. Marc.achen@ludwig.edu.au) . PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Jan 20) 95 (2) 548-53. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB We have identified a member of the VEGF family by computer-based homology searching and have designated it **VEGF-D**. **VEGF -D** is most closely related to VEGF-C by virtue of the presence of N- and C-terminal extensions that are not found in other VEGF family members. In adult human tissues, **VEGF-D** mRNA is most abundant in heart, lung, skeletal muscle, colon, and small intestine. Analyses of **VEGF-D** receptor specificity revealed that **VEGF-D** is a ligand for both VEGF receptors (VEGFRs) VEGFR-2 (Flk1) and VEGFR-3 (Flt4) and can activate these receptors. However. **VEGF-D** does not bind to VEGFR-1. Expression of a truncated derivative of **VEGF-D** demonstrated that the receptor-binding capacities reside in the portion of the molecule that is most closely related in primary structure to other VEGF family members and that corresponds to the mature form of VEGF-C. In addition, **VEGF-D** is a mitogen for endothelial cells. The structural and functional similarities between **VEGF-D** and VEGF-C define a subfamily of the VEGFs.

```
=> d his

     (FILE 'HOME' ENTERED AT 08:27:25 ON 18 JUN 2002)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 08:27:43 ON
     18 JUN 2002
L1         10108 S CYCLIC PEPTIDE
L2            66 S L1 AND MONOMERIC
L3             1 S L2 AND MONOCYCLIC
L4             1 S L2 AND VEGF
L5             1 S L2 AND VEGF-C
L6           288 S VEGF-D
L7             1 S L6 AND CYCLIC PEPTIDE
L8            28 DUP REMOVE L2 (38 DUPLICATES REMOVED)
L9          9964 S (ACHEN M?/AU OR HUGHES R?/AU OR STACKER S?/AU OR CENDRON A?/A
L10           67 S L9 AND VEGF-D
L11            1 S L10 AND CYCLIC PEPTIDE
L12           22 DUP REMOVE L10 (45 DUPLICATES REMOVED)

=> s l9 and VEGFR-2
L13           73 L9 AND VEGFR-2

=> s l13 and VEGFR-3
L14           50 L13 AND VEGFR-3

=> s l14 and inhibitor
L15            2 L14 AND INHIBITOR

=> dup remove l15
PROCESSING COMPLETED FOR L15
L16            1 DUP REMOVE L15 (1 DUPLICATE REMOVED)

=> d l16 cbib abs

L16  ANSWER 1 OF 1     MEDLINE                              DUPLICATE 1
2000247148  Document Number: 20247148.    PubMed ID: 10785369.   Monoclonal
     antibodies to vascular endothelial growth factor-D block its interactions
     with both VEGF receptor-2 and VEGF receptor-3. Achen M G;
     Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A
```

M; Caesar C; Makinen T; Alitalo K; **Stacker S A.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . EUROPEAN JOURNAL OF BIOCHEMISTRY, (2000 May) 267 (9) 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (VEGF-D), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (**VEGFR-2**/Flk1/KDR) and **VEGFR-3** (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. VEGF-D consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human VEGF-D in order to generate VEGF-D antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed VEGF-D. We demonstrate, using bioassays for the binding and cross-linking of **VEGFR-2** and **VEGFR-3** and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature VEGF-D for binding to both **VEGFR-2** and **VEGFR-3** for binding to mature VEGF-D. This indicates that the binding epitopes on VEGF-D for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to VEGF-D. The anti-(VEGF-D) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of VEGF-D.

```
=> s VEGFR-2 and VEGFR-3
L17        260 VEGFR-2 AND VEGFR-3

=> s l17 and inhibitor
L18         25 L17 AND INHIBITOR

=> s l18 and peptide
L19          2 L18 AND PEPTIDE

=> dup remove l19
PROCESSING COMPLETED FOR L19
L20          1 DUP REMOVE L19 (1 DUPLICATE REMOVED)

=> d l20 cbib abs
```

L20 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
2002:279710 Document No.: PREV200200279710. Vascular endothelial growth factor C (VEGF-C) protein and gene, mutants thereof, and uses thereof. Alitalo, Kari (1); Joukov, Vladimir. (1) Helsinki Finland. ASSIGNEE: Licentia Ltd, Helsinki, Finland; Ludwig Institute for Cancer Research. Patent Info.: US 6361946 March 26, 2002. Official Gazette of the United States Patent and Trademark Office Patents, (Mar. 26, 2002) Vol. 1256, No. 4, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133. Language: English.

AB Provided are purified and isolated VEGF-C polypeptides capable of binding to at least one of KDR receptor tyrosine kinase (**VEGFR-2**) and Flt4 receptor tyrosine kinase (**VEGFR-3**); analogs of such **peptides** that have VEGF-C-like or VEGF-like biological activities or that are VEGF or VEGF-C **inhibitors**; polynucleotides encoding the polypeptides; vectors and host cells that embody the polynucleotides; pharmaceutical compositions and diagnostic reagents comprising the polypeptides; and methods of making and using the polypeptides.

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	147.92	148.13

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-14.25	-14.25

STN INTERNATIONAL LOGOFF AT 08:34:46 ON 18 JUN 2002